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α-ADRENOCEPTOR-MEDIATED VASOCONSTRICTION IS NOT INVOLVED IN IMPAIRED FUNCTIONAL VASODILATION IN THE OBESE ZUCKER RAT

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SUMMARY

1. Obesity/metabolic syndrome is associated with augmented α-adrenoceptor sensitivity and impaired hyperaemic responses to exercise. Thus, it is possible that this elevated α-adrenoceptor constriction contributes to the blunted hyperaemic response.

2. Male lean and obese Zucker rats were instrumented for acute measurements of blood pressure (BP) and iliac blood flow (BF). Changes in BP and BF were determined in anaesthetized animals in response to intravenous administration of increasing doses of the α_1-adrenoceptor agonist phenylephrine (PE). Once BF and BP returned to normal, a single bolus of the α-adrenoceptor antagonist phentolamine (0.5 mg) was administered. In separate animals, the spinotrapezius muscle was exteriorized for direct *in situ* observation of the microcirculation in response to phentolamine and muscle contraction.

3. Administration of PE demonstrated that iliac BF is highly autoregulated in the face of increasing perfusion pressure. Iliac conductance following phentolamine was significantly greater in obese rats. Following phentolamine administration, iliac vascular conductance was significantly greater in obese rats compared with lean animals. However, α-adrenoceptor blockade did not significantly alter arteriolar diameter in the spinotrapezius muscle during muscle contraction in either lean or obese animals.

4. These results suggest a greater contribution of the α-adrenoceptors in basal hindlimb vascular tone in obese rats. Furthermore, an augmented α-adrenoceptor-mediated vasoconstriction may not contribute to the impaired functional dilation in anaesthetized obese rats.

Keywords

blood flow; functional hyperaemia; metabolic syndrome; microcirculation; vasoconstriction

INTRODUCTION

The prevalence of obesity in the US has increased steadily over the past decade. Epidemiological reports suggest that approximately 24% of adults in the US over 20 years of age meet the criteria for metabolic syndrome established by the National Cholesterol Education

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Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults III.[1] Metabolic syndrome is a cohort of pathophysiological conditions that includes obesity, insulin resistance, dyslipidaemia and endothelial dysfunction. Based on year 2000 census data, approximately 47 million Americans have metabolic syndrome.[2] There is considerable evidence, both *in vivo*[3] and in isolated artery preparations,[4-7] that obesity/metabolic syndrome is associated with an enhanced reactivity to α-adrenoceptor activation. However, total peripheral resistance (TPR) has been shown to be either higher, similar or lower in obese individuals compared with lean controls.[8-11] Taken together, it is unclear the degree to which α-adrenoceptor-mediated vasoconstriction contributes to the level of basal vascular tone in obese individuals. In addition, individuals and animal models of obesity/metabolic syndrome also exhibit impaired skeletal muscle hyperaemic responses to exercise/muscle contraction, possibly resulting in underperfusion of the active tissue, which may contribute to the exercise intolerance observed in obese patients.[12-15] This impaired hyperaemic response is most likely secondary to the endothelial dysfunction associated with obesity/metabolic syndrome.[14,15] However, it is possible that the enhanced reactivity to vasoconstrictor stimuli contributes to the blunted hyperaemic response by restraining functional hyperaemia.

The obese Zucker rat possesses non-functional leptin receptors and, so, exhibits increased food intake, rapidly developing obesity, insulin resistance, dyslipidaemia and hypertension.[16] Thus, the obese Zucker rat provides a useful tool for the study of vascular function during a cohort of pathophysiological conditions that is rapidly growing in prevalence in humans. Our laboratory has previously demonstrated an augmented α_1-adrenoceptor-mediated vasoconstriction due to Rho kinase-mediated increases in vascular smooth muscle cell Ca^{2+} sensitivity in obese Zucker rats.[4] Moreover, we have also shown a blunted vasodilation in response to muscle contraction in the obese Zucker rat.[14,15] In order to assess the physiological significance of this enhanced α-adrenoceptor vasoconstrictor reactivity observed *in vitro*, we used two distinct types of *in vivo* animal experimental preparations. First, we tested the hypothesis that, in obesity/metabolic syndrome, there is an enhanced role for α-adrenoceptors in the determination of basal vascular tone. Second, we tested the hypothesis that the augmented α_1-adrenoceptor activation restrains the vasodilation in response to muscle contraction.

METHODS

Animals

All animal protocols used in the present study were reviewed and approved by the Institutional Animal Care and Use Committee of the University of Mississippi Medical Center. Male lean (n = 17) and obese (n = 17) rats (age 12–18 weeks; Harlan Teklad, Madison, WI, USA) were used for these experiments.

Determination of α_1-adrenoceptor reactivity and basal adrenergic tone

Rats were anaesthetized using pentobarbital sodium (50 mg/kg, i.p.). In all rats, a carotid artery and an external jugular vein were cannulated for the determination of arterial pressure (BP) and the intravenous infusion of drugs, respectively. For measurement of hindlimb blood flow (BF), a midline laparotomy was performed and an ultrasonic transit-time BF probe (MC1PRB; Transonic, Ithaca, NY, USA) was placed around the right iliac artery; the space between the artery and flow probe was filled with acoustic compliant (Surgilube; Fougera & Co., Melville, NY, USA). The abdomen was closed with monofilament suture. Following a 30 min stabilization period, phenylephrine (PE; 0.1 mg/mL) was infused at 15, 30 and 45 μL/min (3 min/dose). After the infusion of PE was stopped and BP had returned to baseline levels, a single bolus of phentolamine (0.5 mg, i.v.) was administered. Preliminary studies demonstrated that this dose of phentolamine was adequate to inhibit α-adrenoceptors because PE-mediated haemodynamic changes were inhibited (data not shown). In addition, subsequent doses of

phentolamine had no additional effect on BP or BF (data not shown). Because blood volume has been shown to be similar between lean and obese Zucker rats,[3,7] doses of PE and phentolamine were not adjusted for differences in bodyweight between animals, ensuring that the acute circulating concentrations of the drugs being administered were similar between groups. In a separate set of animals, we measured muscle and fat mass in the hindlimb of lean and obese rats (right hindlimb mass 20.4 ± 0.9 and 16.9 ± 0.6 g, respectively; muscle mass 16.1 ± 0.8 and 12.6 ± 0.6 g, respectively; fat mass 0.5 ± 0.1 and 3.2 ± 0.2 g, respectively; bodyweight 313 ± 6 and 467 ± 29 g, respectively). Because we measured iliac blood flow in these experiments, we were measuring the perfusion of both lean and adipose hindlimb tissue. Furthermore, because the additional adipose tissue in obese animals is not associated with a proportional increase in vascularity within the new adipose tissue[17,18] and the vascular density is different between skeletal muscle and adipose tissues, we felt it was inappropriate to normalize BF values to limb mass. Changes in BP and BF were recorded continuously using a PC-based data-acquisition system (Dataq Instruments, Akron, OH, USA) and analysed off-line.

Microcirculatory preparation

The spinotrapezius muscle was prepared for experimental observation as described previously.[14,15,19,20] Briefly, rats were anaesthetized with pentobarbital sodium (50 mg/kg, i.p.) and the trachea was intubated. Animals spontaneously breathed a gas mixture containing 30% oxygen and 70% nitrogen. At all times during the surgery and subsequent experiment, the right spinotrapezius muscle was kept at *in situ* dimensions and superfused continuously with a physiological salt solution (composition (in mmol/L): NaCl 118.07; KCl 6.17; $CaCl_2$ 2.55; $NaHCO_3$ 25) and aerated with a 5% CO_{2-} 95% N_2 gas mixture (pH 7.4, 35°C). The microcirculation of the spinotrapezius muscle was transilluminated and observed under a Nikon (Kanagawa, Japan) microscope fitted with a ×10 long working-distance objective (numerical aperture = 0.30). The microscopic image was televised with a Dage (Madison City, IN, USA) closed-circuit television camera and displayed on a Sony (Tokyo, Japan) monitor. The magnification of the image was ×1000 from the tissue to the monitor screen. Vessel diameter was measured using a Texas A&M (Microcirculatory Research Institute, College Station, TX, USA) video analyser modified to function as a video micrometer. With the use of this device, we positioned two movable lines on the inside of the vessel walls and a DC voltage proportional to the line separation was recorded using a computerized data-collecting system. The resolution of this system was ±1 μm.

Sympathetic restraint of functional vasodilation in the spinotrapezius muscle

Lean and obese animals were allowed to stabilize for 15–30 min after completion of the surgical procedure. A segment of the arteriolar vascular arcade was selected for analysis (basal diameter 14 ± 1 μm). Two hooked silver–silver chloride electrodes (Harvard Instruments, Holliston, MA, USA) were placed at each end of the spinotrapezius and connected to a Grass S44 stimulator (Grass Instruments, West Warwick, RI, USA). Basal diameter and changes in response to muscle contraction (functional vasodilation; 4–5 V, 1 Hz) were recorded for 2 min. Arterioles of the spinotrapezius muscle were then treated for 30 min with phentolamine (10 μmol/L) and the muscle stimulation repeated. Previous work in our laboratory has shown that enhanced thromboxane receptor activation partially mediates the blunted functional vasodilation in the obese Zucker rat.[15] In a separate set of experiments, arterioles of the spinotrapezius muscle were treated for 30 min with the thromboxane receptor antagonist SQ29548 (10 μmol/L) prior to muscle contraction to remove the augmented thromboxane-mediated vasoconstriction observed in obese Zucker rats.[15] To determine the role of ongoing α-adrenoceptor activity after removal of thromboxane-mediated vasoconstriction during continuous muscle contraction, phentolamine (10 μmol/L) was added to the superfusion solution and the change in diameter was recorded.

Drugs and solutions

Phenylephrine (0.1 mg/mL) was dissolved in saline and stored at −20°C until use. Phentolamine (10 mg/mL) was dissolved in water (*in vivo* studies) and prepared fresh daily or dissolved in ethanol (microcirculatory studies) and stored at −20°C until use. All chemicals were purchased from Sigma Chemical (St Louis, MO, USA).

Statistics and data analysis

Data were analysed using Student's *t*-test or two-way repeated-measures analysis of variance. Individual groups were compared using the Holm–Sidak post hoc test. $P \leq 0.05$ was accepted as statistically significant for all comparisons. Data are presented as the mean±SEM. Increases in artery diameter in response to muscle contraction and phentolamine are expressed as percentage vasodilation i.e. ((response – basal)/(maximal – basal)).

RESULTS

Descriptive characteristics and baseline data for animals used in iliac blood flow experiments are presented in Table 1. Bodyweight and resting BP were significantly greater in obese rats compared with lean controls. There were no statistically significant differences between groups for resting heart rate, resting iliac BF or resting vascular conductance.

α_1-Adrenoceptor reactivity and basal adrenergic tone

Figure 1 shows the BP response to the administration of increasing doses of PE. Baseline BP was significantly higher in obese rats compared with lean controls. Phenylephrine elicited significantly greater increases in BP in obese rats compared with control animals for the 15 and 30 μL/min doses (Fig. 1b). Figure 2 shows iliac BF and conductance responses to PE infusion. Using a two-way anova (group (lean or obese) × dose of PE), there were no differences found in BF or conductance in response to PE between groups (non-significant interaction between group and dose). However, two-way ANOVA revealed a significant main effect of PE dose. Phenylephrine did not significantly alter iliac BF at either 15 or 30 μL/min. Contrary to our expectations, BF was increased significantly at the highest doses of PE for lean and obese combined (Fig. 2a). Administration of PE at a rate of 15 μL/min significantly reduced vascular conductance in the collapsed group (lean + obese). Subsequent doses of PE failed to elicit further reductions in vascular conductance. Conductance during infusion of 45 μL/min PE was significantly greater than during the preceding dose of PE for lean and obese combined (Fig. 2b). Heart rate decreased in a dose-dependent manner in response to graded infusions of PE in lean animals. Consistent with previous work,[21-23] baroreflex-mediated bradycardic responses to PE administration were blunted in obese animals (Fig. 3).

Intravenous administration of phentolamine produced a significantly greater decrease in BP in obese rats than in lean controls (54 ± 6 and 34 ± 5 mmHg, respectively), although the absolute BP was similar between groups (83 ± 6 and 75 ± 6 mmHg, respectively). Figure 4 shows changes in iliac vascular conductance in response to the systemic administration of phentolamine. Baseline iliac conductance prior to phentolamine administration was no different between lean and obese rats (Fig. 4). Five minutes after phentolamine administration, iliac vascular conductance was significantly greater in obese rats compared with controls (Fig. 4).

Adrenergic restraint of functional vasodilation

In the spinotrapezius muscle preparation, muscle contraction under control conditions produced an increase in arteriolar diameter that was significantly blunted in obese rats (Figs 5,6a). Inhibition of α-adrenoceptors did not augment the vasodilation in response to muscle

contraction in either lean or obese animals (Fig. 5). In arteries treated with SQ29548, the addition of phentolamine to the superfusion solution during muscle contraction did not significantly increase diameter in either group (Fig. 6b). The maximal arteriolar diameter (10 μmol/L adenosine) for lean and obese rats was 41 ± 1 and 48 ± 2 μm, respectively.

DISCUSSION

The present study was designed to investigate whether there is an enhanced contribution of the α-adrenoceptor system in determining the level of basal tone in obese Zucker rats. Based on our results, we also investigated whether an augmented α-adrenoceptor-mediated vasoconstriction would attenuate the vasodilation in response to muscle contraction. The major findings of the present study are as follows: (i) PE elicited greater increases in BP in obese rats compared with lean controls; (ii) iliac BF was nearly perfectly autoregulated during PE infusion; (iii) iliac conductance was significantly elevated in obese rats compared with lean controls following α-adrenoceptor blockade; and (iv) α-adrenoceptor activity during muscle contraction was absent in both lean and obese animals.

In the present study, the BP response curve to PE was shifted to the left in obese rats compared with lean controls. This is consistent with numerous studies using isolated resistance arteries demonstrating an enhanced α_1-adrenoceptor-mediated vasoconstriction in obese animals compared with lean controls.[4,5] Alternatively, the augmented BP response to PE administration could be due to a blunted baroreflex response in the obese Zucker rat.[23] We have shown that iliac BF (and conductance) remained roughly constant during PE infusion. The diminished response to PE may be due to an ongoing endogenous activation of the receptors. Moreover, these results suggest that the hindlimb vasculature is tightly autoregulated, maintaining BF in the face of elevated perfusion pressure. The higher perfusion pressure in obese rats would necessitate a greater degree of vasoconstriction (adrenergic, myogenic or both) in order to maintain BF. Furthermore, these results suggest that other vasculature beds (e.g. splanchnic) may be a major source of the increase in vascular resistance (and hence BP) in response to PE in anaesthetized Zucker rats.

There is considerable evidence that obesity is associated with elevated sympathetic nerve activity (SNA).[24-26] Indeed, renal SNA is significantly greater in obese Zucker rats.[27] Consistent with the present study, Carlson *et al*. demonstrated that ganglionic block produces a greater fall in mean arterial pressure in obese Zucker rats compared with lean animals.[28] However, whether this increased SNA results in an enhanced contribution of the autonomic nervous system in determining the degree of basal vascular tone is unclear. In the present study, we observed that BP was significantly higher in obese rats compared with lean controls, whereas following α-adrenoceptor blockade, absolute mean arterial BP was similar between lean and obese rats. In addition, iliac conductance following phentolamine administration was significantly elevated in obese rats compared with lean controls. Taken together, these results suggest the α-adrenoceptors play a more prominent role in determining basal vascular tone in obese animals compared with lean controls. This enhanced α-adrenoceptor-mediated vasoconstriction in anaesthetized Zucker rats may be the result of an increased SNA, an augmented α-adrenoceptor sensitivity[4,5] or both.

Consistent with our previous studies,[14,15] we also demonstrated that functional vasodilation is blunted in obese animals relative to lean controls. However, adrenergic restraint of the vasodilation does not appear to be involved in the observed impaired functional vasodilation in the spinotrapezius muscle of the obese Zucker rat because the administration of phentolamine during muscle contraction failed to elicit significant increases in arteriolar diameter in either group. These results are in opposition to a series of studies by Frisbee's laboratory suggesting an α-adrenoceptor restraint of the vasodilatory responses to hypoxia[29]

and muscle contraction.[29,30] However, in those studies the investigators administered systemic α-adrenoceptor block prior to the vasodilator stimulus. Thus, the vasodilation was elicited during a lower perfusion pressure. Therefore, the augmented vasodilation observed in those studies may be due to an increased autoregulatory vasodilation rather than an effect secondary to removal of a vasoconstrictor stimulus. In the present study, phentolamine was administered during local muscle contraction through the superfusion solution to determine the degree of ongoing adrenergic-mediated vasoconstriction during the muscle contraction. Consistent with the present study, previous studies have suggested that α-adrenoceptor reactivity is blunted in an intensity dependent manner during exercise[31] and that α-adrenoceptor-mediated vasoconstriction diminishes with increasing workload,[29,32] a phenomenon referred to as 'sympatholysis'.

Limitations

A potential constraint of our experimental approach is that we used local muscle contraction rather than conscious whole-body exercise; indeed, there is evidence that SNA rises during exercise.[33,34] Thus, there may be a greater effect of phentolamine during whole-body exercise than in our isolated *in situ* muscle preparation. In addition, we only examined one submaximal level of muscle stimulation. With lower-intensity muscle contraction, α-adrenoceptor activity may contribute to the impaired functional dilation in obese Zucker rats. In addition, it is possible that the use of pentobarbital sodium anaesthesia in these experiments suppressed the level of tonic sympathetic activation, reducing any potential contribution of the sympathetic nervous system to the blunted functional vasodilation in obese Zucker rats. Taken together, these results suggest that the blunted functional vasodilation observed in the anaesthetized obese Zucker rat may not be the result of α-adrenoceptor-mediated vasoconstriction, but is possibly secondary to endothelial dysfunction.[15] Another potential limitation is the assumption that the degree of adrenergic activity during muscle contraction is similar between the spinotrapezius and hindlimb muscles. Indeed, there is considerable vascular heterogeneity between muscles of the arms and legs in humans.[35] The spinotrapezius m. is a mixed-fibre (41% type I, 7% type IIa and 17% type IIB) skeletal muscle involved in stabilizing the scapula and is recruited during downhill running.[36] Although we cannot exclude the possibility that adrenergic activity to other skeletal muscle beds differs from that of the spinotrapezius muscle, the spinotrapezius is a flat muscle of mixed fibre composition involved in both postural control and locomotion. In addition, a strength of our approach is the use of intravital microscopy, which allows direct observation of the vasculature. Again, this can only be performed in a thin, flat muscle, which makes the spinotrapezius muscle ideally suited for this approach. Thus, the spinotrapezius serves as a good model for direct observation of the microcirculation of skeletal muscle.

Conclusions

In conclusion, the results of the present study suggest a greater role of the sympathetic nervous system in the determination of basal hindlimb vascular tone and that the impaired functional vasodilation in obese rats may not be due to an augmented α-adrenoceptor-mediated vasoconstriction. Thus, the exercise intolerance seen in obese/metabolic syndrome individuals is most likely secondary to an increased workload during exercise due to increased body mass, decreased glucose utilization (insulin resistance) and/or endothelial dysfunction (impaired functional vasodilation).

Acknowledgments

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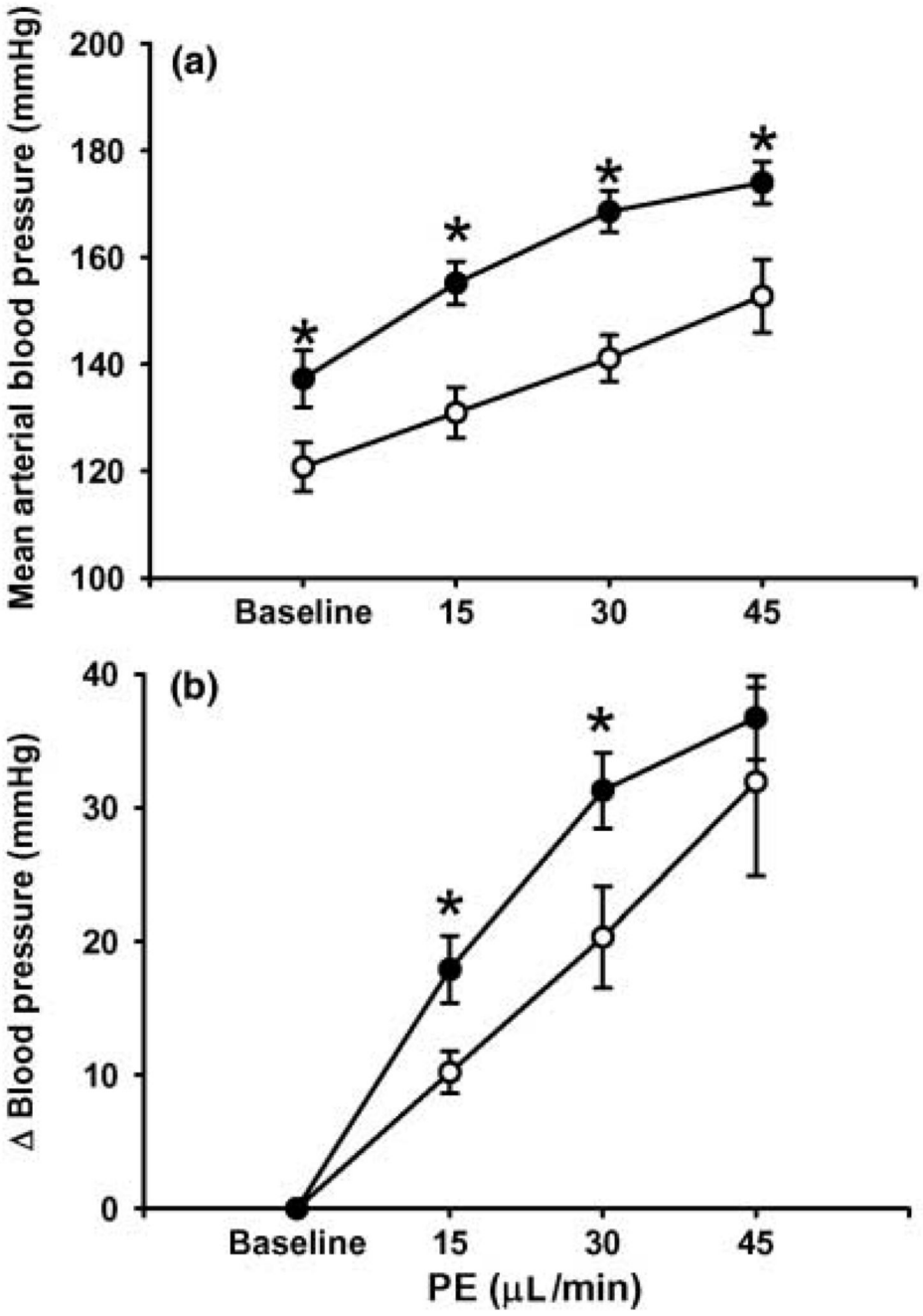

Fig. 1.

(a) Blood pressure and (b) changes in blood pressure in response to graded infusions of phenylephrine (PE) in lean ($n = 5$; ○) and obese ($n = 5$; ●) rats. Data are presented as the mean ±SEM. *$P < 0.05$ compared with obese rats.

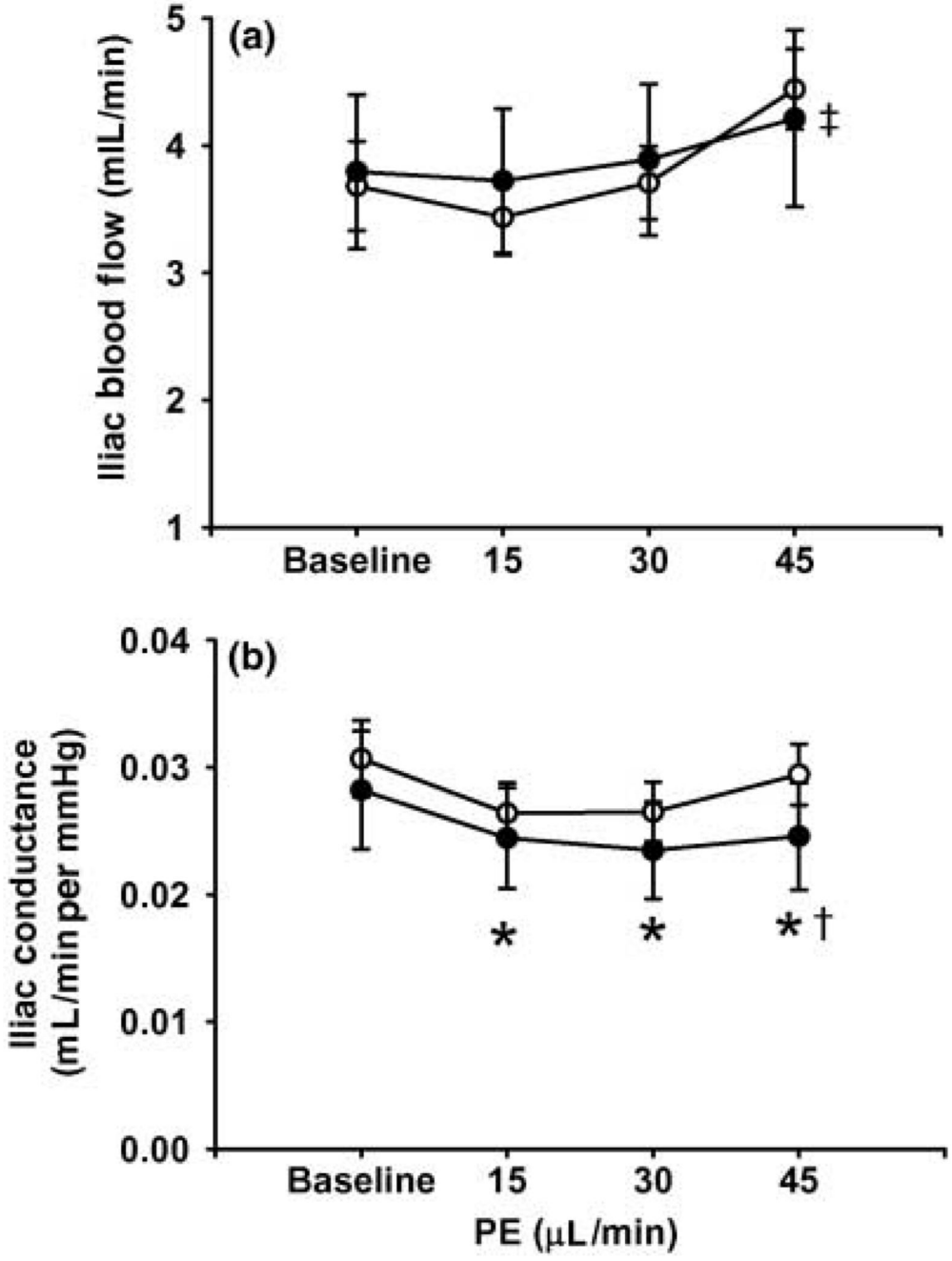

Fig. 2.

Iliac (a) blood flow and (b) conductance in response to graded infusions of phenylephrine (PE) in lean ($n = 5$; ○) and obese ($n = 5$; ●) rats. Data are presented as the mean±SEM. *$P < 0.05$ compared with baseline for lean and obese combined (main effect of dose); $^{\dagger}P < 0.05$ compared with 30 μL/min PE for lean and obese combined; $^{\ddagger}P < 0.05$ comapred with baseline and 15 and 30 μL/min PE for lean and obese combined.

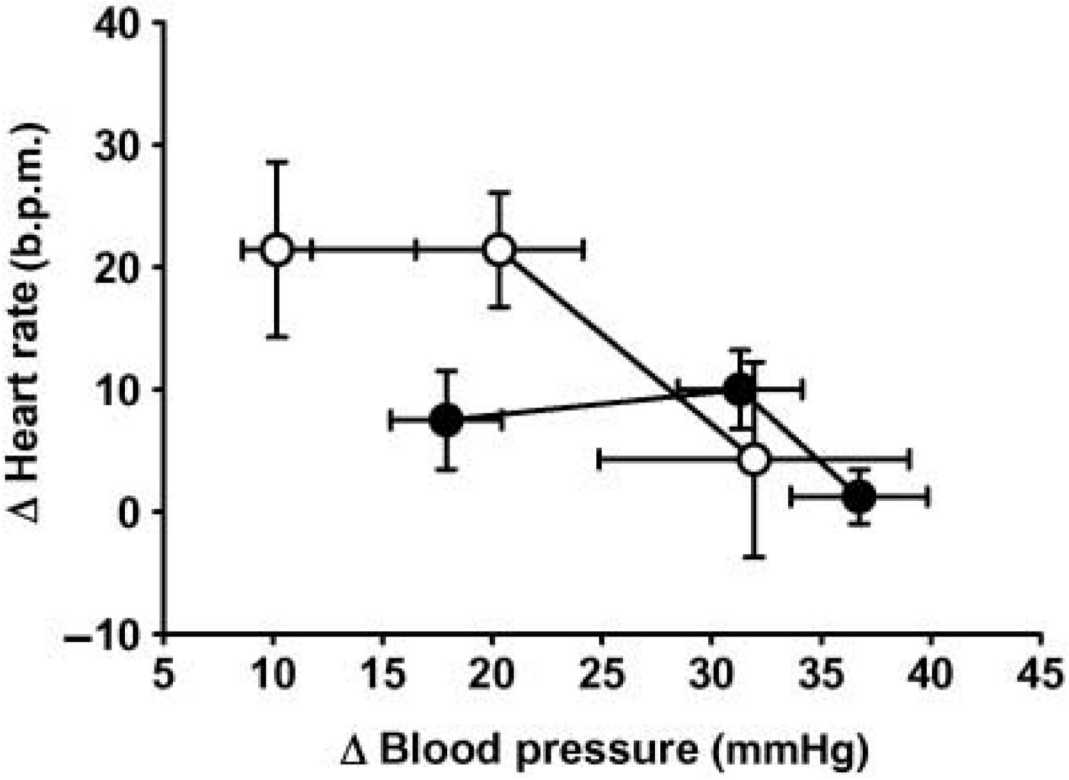

Fig. 3.
Baroreflex responses to phenylephrine are blunted in obese rats (●) compared with lean (○) animals. Data are presented as the mean±SEM (*n* = 5/group).

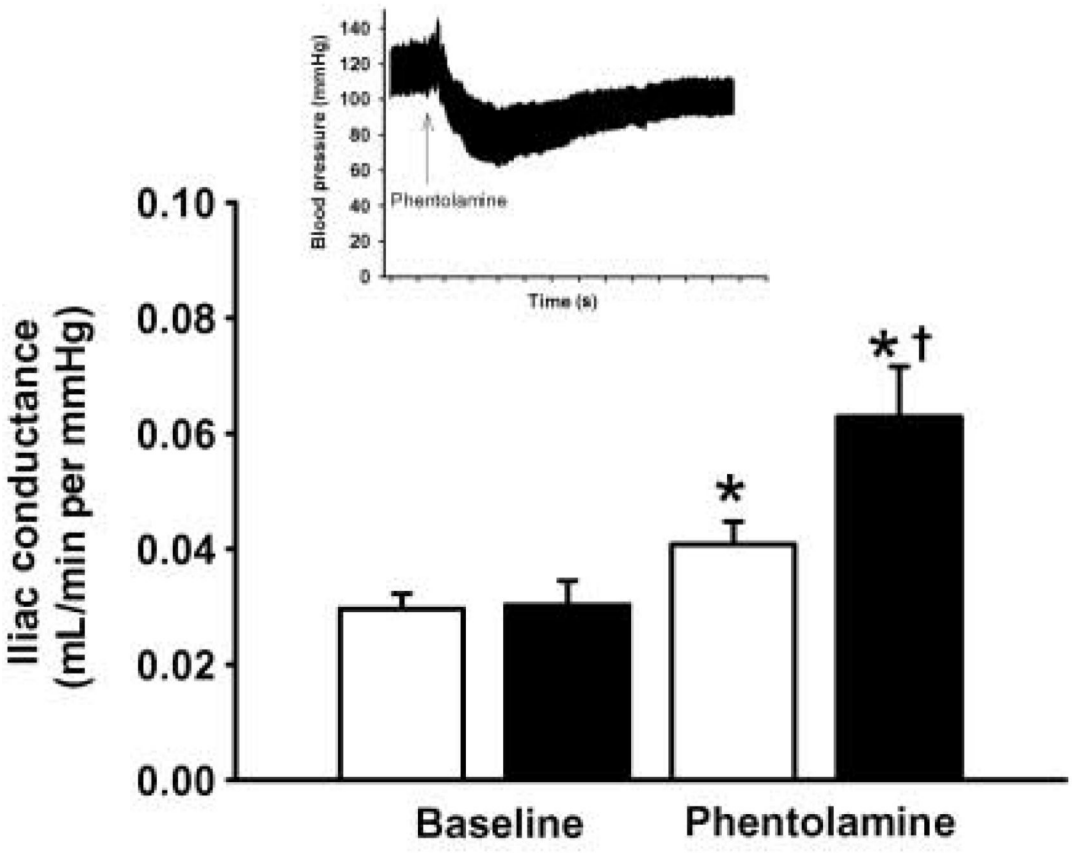

Fig. 4.

Effect of α-adrenoceptor blockade on iliac vascular conductance in lean (□) and obese (■) rats. Data are presented as the mean±SEM (n = 5 per group). Inset: raw trace of the blood pressure response to phentolamine. *P < 0.05 compared with baseline; $^{\dagger}P$ < 0.05 compared with lean rats after phentolamine administration (P < 0.05).

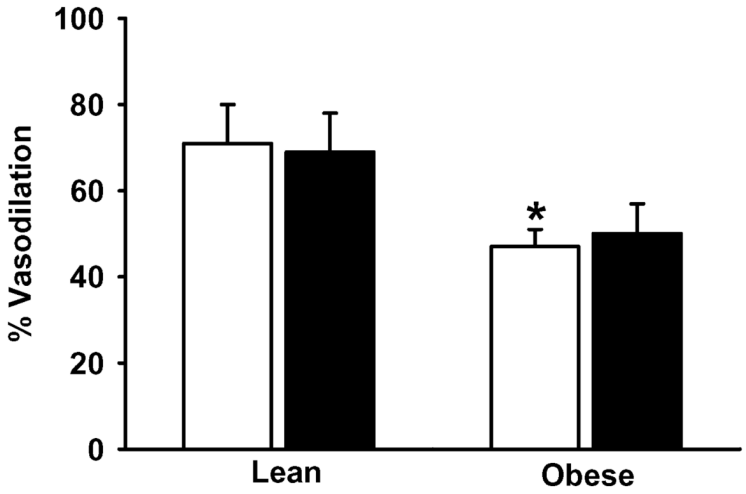

Fig. 5.

Effect of α-adrenoceptor inhibition on functional vasodilation in lean and obese rats. The spinotrapezius muscle was treated with phentolamine (10 μmol/L; ■;) for 30 min. (□), control. Data are presented as the mean±SEM (n = 4 per group). *P < 0.05 compared with lean control.

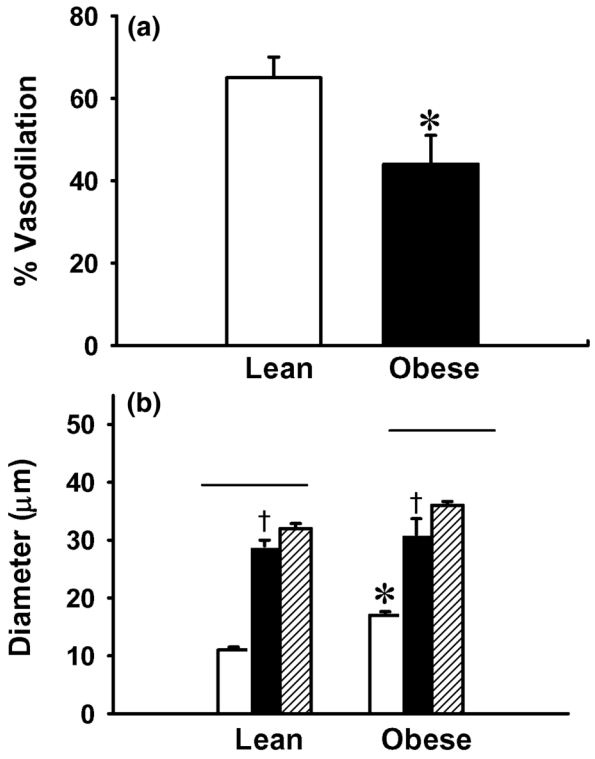

Fig. 6.

Vasodilation in response to contraction of the spinotrapezius muscle in anaesthetized lean and obese Zucker rats. (a) Functional vasodilation of arterioles in the spinotrapezius muscle prior to phentolamine administration in lean and obese rats. (b) Changes in arteriole diameter in response to muscle contraction (■;) and phentolamine + muscle contraction (▨) in the spinotrapezius muscle of lean and obese rats. (□), baseline. Arterioles were pretreated with SQ29548 (10 μmol/L) for 30 min. Data are presented as the mean±SEM (n = 4 per group). *$P < 0.05$ compared with lean control; †$P < 0.05$ compared with baseline. Bars indicate maximal diameter (10 μmol/L adenosine induced).

Table 1

Descriptive characteristics and baseline values of rats used for iliac blood flow measurements

	Bodyweight (g)	Heart rate (b.p.m.)	Resting BP (mmHg)	Iliac BF (mL/min)	Basal hindlimb conductance (mL/min per mmHg)
Lean	394 ± 13	427 ± 10	121 ± 5	3.68 ± 0.35	0.031 ± 0.003
Obese	627 ± 18*	426 ± 15	137 ± 5*	3.79 ± 0.60	0.028 ± 0.005

Data are the mean±SEM.

BP, blood pressure; BF, blood flow.

*$P < 0.05$ compared with lean animals.